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TI TrkA cross-linking mimics neuronal responses to nerve growth factor.
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AB TrkA, a tyrosine kinase receptor, is an essential component of the nerve growth factor (NGF) response pathway. The binding of NGF to the receptor induces receptor autophosphorylation and activation of intracellular signaling pathways, resulting in diverse biological effects. We prepared polyclonal antibodies against the entire extracellular domain of rat trkA produced using a baculovirus expression system. These antibodies specifically recognize rat trkA on antigen blots and in immunoprecipitations. Both IgG and Fab fragments block binding of NGF to trkA expressed by the PC12 cell line. In NGF binding studies using anti-trkA and anti-low-affinity NGF receptor (LNGFR) immunoglobulin (Ig) G, essentially all binding of NGF can be inhibited. The results imply that > or = 97% of the NGF binding sites on PC12 cells are accounted for by trkA and the LNGFR. The binding data also argue that all low-affinity NGF binding sites on PC12 cells reflect interactions with the LNGFR, while all high-affinity sites are trkA dependent. A fraction of the high-affinity (or slow) binding sites seem to require both trkA and the LNGFR. Although the monovalent anti-trkA Fab fragments inhibited the biological effects of NGF, such as induction of tyrosine phosphorylation, and survival and neurite outgrowth of sympathetic neurons, the IgG preparation was not effective as an inhibitor. Instead, the IgG fraction by itself was almost as effective as NGF at stimulating receptor activation, cell survival, and neurite outgrowth. Thus, it appears oligomerization of trkA by antibody-induced cross-linking is sufficient to produce the known cellular effects of NGF.